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PERSPECTIVE

Risks and Benefits of Gene Therapy

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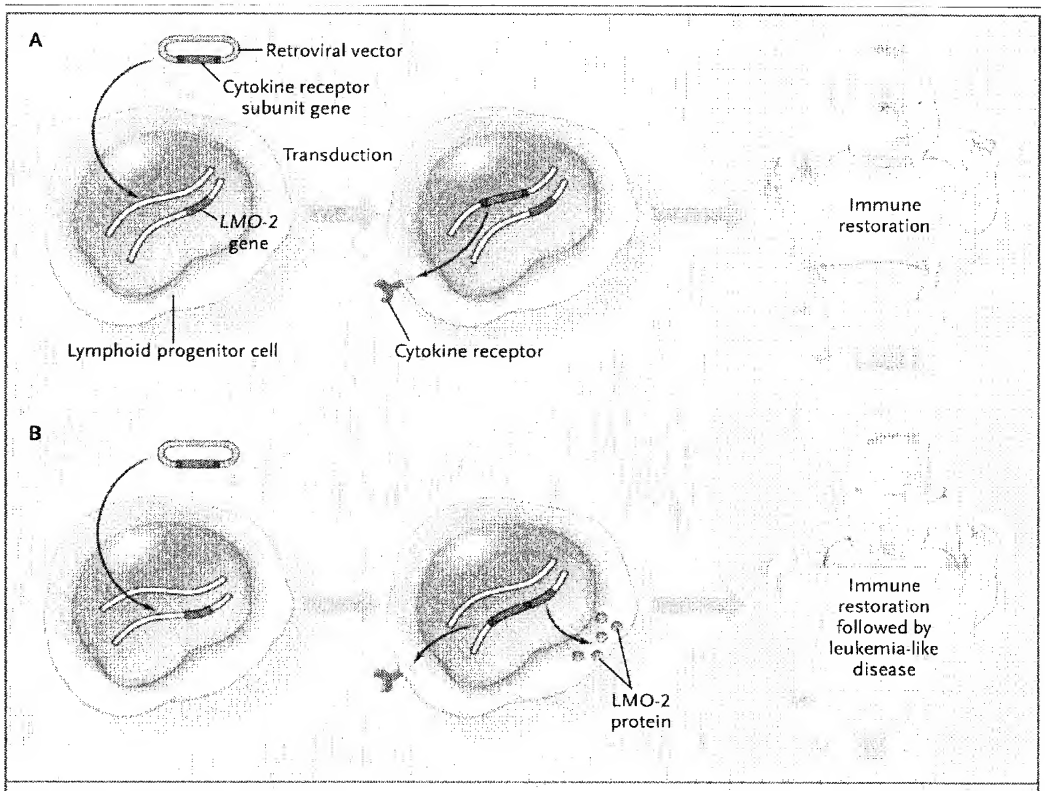
Although most of today's gene-therapy trials are targeted to cancer, there is renewed interest in pursuing the goal for which gene therapy was invented: the cure of genetic disease. Recent studies from France, the United Kingdom, and Italy have provided encouraging results in the treatment of several forms of a rare, devastating disease of infancy, collectively called severe combined immunodeficiency. Each form of this disease is caused by a mutation in a single gene. In these studies, a modified retrovirus was used to insert, in vitro, a "corrective" gene into the host genome. "Corrected" cells were then returned to the patients, in whom an immune response subsequently developed (see Panel A of Figure). In a letter in this issue of the *Journal* (pages 255–256), however, Hacein-Bey and colleagues describe a serious adverse event — a leukemia-like disorder — in a young child, 30 months after a single gene-therapy treatment.

When Hacein-Bey and colleagues first suspected a problem during the trial in early September, they immediately informed the families of the patients. They also shared data with other investigators of similar gene-therapy trials, members of the broader gene-therapy community, and regulatory agencies. As a precaution, the Food and Drug Administration (FDA) put three similar gene-therapy trials on hold, and its Biological Response Modifiers Advisory Committee met in mid-October to discuss the future of gene-therapy trials for severe combined immunodeficiency in the United States.

The committee concluded that the molecular event that provided clinical benefit in the gene therapy tested by Hacein-Bey and colleagues was also the probable cause of the leukemia-like adverse event (see Panel B of Figure) and made some recommendations. It recommended that retroviral gene-transfer trials for severe combined immunodeficiency in the United States be allowed to proceed, but with careful attention to inclusion and exclusion criteria, so as to provide the best ratio of benefit to risk, relative to other therapies. Related to this is the revision of consent documents. Children with severe combined immunodeficiency who have an HLA-identical donor should be excluded from gene-therapy trials because of the high success rate of bone marrow transplantation from a fully matched donor (greater than 90 percent success). But the trials should be available to children with severe combined immunodeficiency in whom transplantation from an HLA-identical donor fails and to those who do not have an HLA-identical donor (about 80 percent of the cases).

This relatively permissive response is based on the advantage of a successful treatment for severe combined immunodeficiency — reported clinical benefits that seem to be more robust than those associated with HLA-identical marrow transplantation — balanced against an as yet unquantifiable risk of the development of leukemia from insertional mutagenesis. The parents of children with severe combined immunodeficiency felt strongly about this point and argued that it is better that parents or guardians have the option to make an informed choice than to have no choice at all.

Because retroviral vectors are thought to insert themselves at random positions in the host genome, insertional mutagenesis as a potential risk of retroviral gene therapy has been debated for some years. That an instance of insertional mutagenesis first happened in humans during a clinical trial surprised some, but not those of us who regulate biologic products such as gene therapy. We take to heart the words of Robert Ingersoll: "In nature there are no rewards or punishments; there are consequences." Gene therapies are constructs derived from nature; they are not of nature. The manipulations needed to create genetic therapy add enormous complexity to considerations of safety and preclinical toxicity testing, and for every intended



Misfiring of Gene Therapy.

By inserting a viral-derived cassette containing a gene encoding a subunit of a human cytokine receptor into the DNA of patients' receptor-deficient blood cells, Hacein-Bey and colleagues obtained "corrected" cells with functional cytokine receptors (Panel A). Transfusion of the corrected cells into the patients resulted in a full restoration of immune function. However, one patient was recently found to have a dramatic increase in circulating mature T cells, a feature reminiscent of lymphocytic leukemia. Analysis of the lymphocytes showed that the gene encoding the cytokine receptor subunit had been inserted in the immediate vicinity of another gene, *LMO-2*, and that elevated levels of LMO-2 protein were being expressed (red circles in Panel B). It seems likely that the increased expression of LMO-2 contributed to the leukemia-like disease, because the protein has previously been implicated in T-cell leukemia.

consequence of a complex biologic product, there are unintended consequences. Biologic products, like all products, carry risks along with benefits.

Tractable diseases have been taken care of; those that have resisted more conventional approaches, such as severe combined immunodeficiency, are now being tackled. Each therapeutic effort that shows potential benefit needs to be scrutinized closely, with the knowledge that most clinical trials fail to show benefit. We must remember that the evolution of medical practice is dynamic. As each new, unexpected adverse event arises, evaluation is carried out again and again, and in the process, new scientific ideas unfold that ultimately yield medically useful products.

From the Food and Drug Administration, Rockville, Md.